IN THE SPECIFICATION:

Please amend the specification as follows:

On page 1, please amend the title of the application beginning on line 4 as follows:

METHODS OF TREATING INFLAMMATORY OR AUTOIMMUNE DISORDERS BY ADMINISTERING CD2 ~~ANTAGONISTS~~ BINDING MOLECULES IN COMBINATION WITH ~~OTHER PROPHYLACTIC OR THERAPEUTIC AGENTS~~ ANTI-ANGIOGENIC AGENTS

On page 9, please amend the paragraph beginning on line 3 as follows:

The prophylactic or therapeutic agents of the combination therapies of the invention can be administered to a subject concurrently. The term "concurrently" is not limited to the administration of prophylactic or therapeutic agents at exactly the same time, but rather it is meant that a CD2 antagonist and the other agent are administered to a subject in a sequence and within a time interval such that the CD2 antagonist can act together with the other agent to provide an increased benefit than if they were administered otherwise. For example, each prophylactic or therapeutic agent (e.g., MEDI-507, an anti-angiogenic agent (e.g., VITAXIN™, ~~REMICADE™~~ REMICADE® (infliximab), or ~~ENBREL™~~ ENBREL® (etanercept)), an anti-inflammatory agent, a dermatological agent, or an immunomodulatory agent such as a cytokine receptor modulator or T cell receptor modulator) may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each prophylactic or therapeutic agent can be administered separately, in any appropriate form and by any suitable route. In various embodiments, the prophylactic or therapeutic agents are administered less than 15 minutes, less than 30 minutes, less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In preferred embodiments, two or more prophylactic or therapeutic agents are administered within the same patient visit.

On page 28, please amend the paragraph beginning on line 21 as follows:

In another embodiment, an article of manufacture comprises packaging material and a pharmaceutical composition in suitable form for administration to a subject, preferably a human, and most preferably a human with an autoimmune or inflammatory disorder, contained within said packaging material, wherein said pharmaceutical composition comprises a CD2 antagonist, a TNF-α antagonist, and a pharmaceutically acceptable carrier. In a preferred embodiment, an article of manufacture comprises packaging material and a pharmaceutical composition in suitable form for administration to a human, preferably a human with an autoimmune or inflammatory disorder, contained within said packaging material, wherein said pharmaceutical composition comprises a CD2 antagonist, a ~~ENBREL™~~ENBREL® (etanercept) or ~~REMICADE™~~REMICADE® (infliximab), and a pharmaceutically acceptable carrier. In accordance with these embodiments, preferably the CD2 antagonist is a CD2 binding molecule and more preferably the CD2 antagonist is MEDI-507 or an antigen-binding fragment thereof.

On page 31, please amend the paragraph beginning on line 19 as follows:

As used herein, the terms "anti-TNF-α agent", "TNF-α antagonists" and analogous terms refer to any protein, polypeptide, peptide, fusion protein, antibody, antibody fragment, large molecule, or small molecule that blocks, reduces, inhibits or neutralizes the function, activity and/or expression of tumor necrosis alpha (TNF-α). Examples of TNF-α ~~antogonists~~antagonists include, but are not limited to, ~~REMICADE™~~REMICADE® (infliximab) and ~~ENBREL™~~ENBREL® (etanercept). In various embodiments, a TNF-α antagonist reduces the function, activity and/or expression of TNF-α by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% relative to control such as phosphate buffered saline (PBS).

On page 40, please amend the paragraph beginning on line 20 as follows:

As used herein, the phrase "side effects" encompasses unwanted and adverse effects of a prophylactic or therapeutic agent. Adverse effects are always unwanted, but unwanted effets are not necessarily adverse. An adverse effect from a prophylactic or therapeutic agent might be harmful or uncomfortable or risky. Side effects from administration of ~~REMICADE™~~REMICADE® (infliximab) include, but are not limited to, risk of serious

infection and hypersensitivity reactions. Other side effects range from nonspecific symptoms such as fever or chills, pruritus or urticaria, and cardiopulmonary reactions such as chest pain, hypotension, hypertension or dyspnea, to effects such as myalgia and/or arthralgia, rash, facial, hand or lip edema, dysphagia, sore throat, and headache. Yet other side effects include, but are not limited to, abdominal hernia, splenic infarction, splenomegaly, dizziness, upper motor neuron lesions, lupus erythematosus syndrome, rheumatoid nodules, ceruminosis, abdominal pain, diarrhea, gastric ulcers, intestinal obstruction, intestinal perforation, intestinal stenosis, nausea, pancreatitis, vomiting, back pain, bone fracture, tendon disorder or injury, cardiac failure, myocardial ischema, lymphoma, thromobocytopenia, cellulitis, anxiety, confusion, delirium, depression, somnolence, suicide attempts, anemia, abscess, bacterial infections, and sepsis. Side effects from administration of ~~ENBREL™~~ENBREL® (etanercept) include, but are not limited to, risk of serious infection and sepsis, including fatalities. Adverse side effects range from serious infections such as pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, sepsis, headache, nausea, rhinitis, dizziness, pharyngitis, cough, asthenia, abdominal pain, rash, peripheral edema, respirator disorder dyspepsia, sinusitis, vomiting, mouth ulcer, alopecia, and pheumonitis to other less frequent adverse effects such as heart failure, myocardial infarction, myocardia ischemia, cerebral ischemia, ~~hyertension~~hypertension, hypotension, cholcystitis, pancreatitis, gastrointestinal hemorrhage, bursitis, depression, dyspnea, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, and thrombophlebitis. The side effects resulting from administration of methotrexate include, but are not lmited to, serious toxic reactions, which can be fatal, such as unexpectedly severe bone marrow suppression, gastrointestinal toxicity, hepatotoxicity, fibrosis and cirrhosis after prolonged use, lung diseases, diarrhea and ulcerative stomatitis, malignant lymphomas and occasionally fatal severe skin reactions.

On page 45, please amend the paragraph beginning on line 16 as follows:

The prophylactic or therapeutic agents of the combination therapies of the invention can be administered to a subject concurrently. The term "concurrently" is not limited to the administration of prophylactic or therapeutic agents at exactly the same time, but rather it is meant that a CD2 antagonist and the other agent are administered to a subject in a sequence and within a time interval such that the CD2 antagonist can act together with the other agent to provide an increased benefit than if they were administered otherwise. For example, each

prophylactic or therapeutic agent (e.g., MEDI-507, an anti-angiogenic agent (e.g., VITAXIN™, ~~REMICADE™~~ REMICADE® (infliximab), or ~~ENBREL™~~ ENBREL® (etanercept)), an anti-inflammatory agent, a dermatological agent, or an immunomodulatory agent such as a cytokine receptor modulator or T cell receptor modulator) may be administered at the same time or sequentially in any order at different points in time; however, if not administered at the same time, they should be administered sufficiently close in time so as to provide the desired therapeutic or prophylactic effect. Each prophylactic or therapeutic agent can be administered separately, in any appropriate form and by any suitable route. In various embodiments, the prophylactic or therapeutic agents are administered less than 15 minutes, less than 30 minutes, less than 1 hour apart, at about 1 hour apart, at about 1 hour to about 2 hours apart, at about 2 hours to about 3 hours apart, at about 3 hours to about 4 hours apart, at about 4 hours to about 5 hours apart, at about 5 hours to about 6 hours apart, at about 6 hours to about 7 hours apart, at about 7 hours to about 8 hours apart, at about 8 hours to about 9 hours apart, at about 9 hours to about 10 hours apart, at about 10 hours to about 11 hours apart, at about 11 hours to about 12 hours apart, no more than 24 hours apart or no more than 48 hours apart. In preferred embodiments, two or more prophylactic or therapeutic agents are administered within the same patient visit.

On page 51, please amend the paragraph beginning on line 24 as follows:

The present invention provides methods for preventing, treating, managing or ameliorating an autoimmune or inflammatory disorder or one or more symptoms thereof, said methods comprising administering to a subject in need thereof one or more CD2 antagonists and one or more anti-angiogenic agents. Preferably, at least one CD2 antagonist is a CD2 binding molecule and more preferably, at least one CD2 antagonist is MEDI-507 or an antigen-binding fragment thereof. Examples of anti-angiogenic agents include, but are not limited to, TNF-α antagonists (*e.g.*, ~~ENBREL™~~ENBREL® (etanercept) or ~~REMICADE™~~REMICADE® (infliximab)), integrin $\alpha_v\beta_3$ antagonists (*e.g.*, VITAXIN™ or antigen-binding fragments thereof), VEGR antagonists, RGD containing peptides, and endostatin.

On page 99, please amend the paragraph beginning on line 3 as follows:

Examples of antibodies that immunospecifically bind to TNF-α include, but are not limited to, infliximab (~~REMICADE®~~REMICADE®; ~~Centacor~~Centocor), D2E7 (Abbott Laboratories/Knoll Pharmaceuticals Col, Mt. Olive, N.J.), CDP571 which is also known as

HUMICADE™ and CDP-870 (both of Celltech/Pharmacia, Slough, U.K.), and TN3-19.12 (Williams et al., 1994, Proc. Natl. Acad. Sci. USA 91: 2762-2766; Thorbecke et al., 1992, Proc. Natl. Acad. Sci. USA 89:7375-7379). The present invention also encompases the use of antibodies that immunospecifically bind to TNF-α disclosed in the following U.S. Patents in the compositions and methods of the invention: 5,136,021; 5,147,638; 5,223,395; 5,231,024; 5,334,380; 5,360,716; 5,426,181; 5,436,154; 5,610,279; 5,644,034; 5,656,272; 5,658,746; 5,698,195; 5,736,138; 5,741,488; 5,808,029; 5,919,452; 5,958,412; 5,959,087; 5,968,741; 5,994,510; 6,036,978; 6,114,517; and 6,171,787; each of which are herein incorporated by reference in their entirety. Examples of soluble TNF-α receptors include, but are not limited to sTNF-R1 (Amgen), etanercept (~~ENBREL™~~ENBREL®; Immunex) and its rat homolog RENBREL™, soluble inhibitors of TNF-α derived from TNFrI, TNFrII (Kohno et al., 1990, Proc. Natl. Acad. Sci. USA 87:8331-8335), and TNF-α Inh (Seckinger et al, 1990, Proc. Natl. Acad. Sci. USA 87:5188-5192).

On page 99, please amend the paragraph beginning on line 19 as follows:

In one embodiment, a TNF-α antagonist used in the compositions and methods of the invention is a soluble TNF-α receptor. In a specific embodiment, a TNF-α antagonist used in the compositions and methods of the invention is etanercept (~~ENBREL™~~ENBREL®; Immunex) or a fragment, derivative or analog thereof. In another embodiment, a TNF-α antagonist used in the compositions and methods of the invention is an antibody that immunospecifically binds to TNF-α. In a specific embodiment, a TNF-α antagonist used in the compositions and methods of the invention is infliximab (~~REMICADE®~~REMICADE®; ~~Centacor~~Centocor) a derivative, analog or antigen-binding fragment thereof.

On page 118, please amend the paragraph beginning on line 27 as follows:

The combination therapies of the invention comprise a CD2 antagonist and at least one other prophylactic or therapeutic agent which has a different mechanism of action than the CD2 antagonist. The mechanisms of prophylactic or therapeutic agents other than CD2 binding molecules which can be used in the combination therapies of the present invention can be found in the art (see, e.g., Hardman et al., eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York at pages 1593-1616, Physician's Desk Reference (PDR) 55.sup.th Ed., 2001, Medical Economics Co., Inc., Montvale, N.J. (~~www.pdr.net~~), and the emedicine website. The combination therapies of the present invention also comprise a CD2 binding molecule and at least one other

prophylactic or therapeutic agent which improves the prophylactic or therapeutic effect of the CD2 antagonist by functioning together with the CD2 antagonist to have an additive or synergistic effect.

On page 121, please amend the paragaph beginning on line 21 as follows:

In a specific embodiment, one or more CD2 binding molecules are administered to a subject, preferably human, with psoriasis prior to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 5 days, 1 week, 2 weeks, 1 month or more before), subsequent to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 5 days, 1 week, 2 weeks, 1 month or more after), or concomitantly with the administration of Xanelim (Genentech/Xoma), ~~Enbril~~ENBREL® (etanercept) (Immunex, Inc.), ~~Remicade~~REMICADE® (infliximab) (J&J/Centocor), ABX-IL-8 (Abgenix), IDEC-114 (IDEC Pharmaceuticals, Inc.), Novim (PDL, Inc.), and/or Zenapax (PDL, Inc.). In another embodiment, an antibody that immunospecifically binds to a CD2 polypeptide is administered to a subject, preferably a human, with psoriasis prior to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 5 days, 1 week, 2 weeks, 1 month or more before), subsequent to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 5 days, 1 week, 2 weeks, 1 month or more after), or concomitantly with the administration of Amevive (Biogen, Inc.). In another embodiment, MEDI-507 is administered to a subject, preferably a human, with psoriasis prior to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 5 days, 1 week, 2 weeks, 1 month or more before), subsequent to (*e.g.*, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 36 hours, 48 hours, 5 days, 1 week, 2 weeks, 1 month or more after), or concomitantly with the administration of Amevive (Biogen, Inc.).

On page 127, please amend the paragraph beginning on line 20 as follows:

In another embodiment, a composition comprises one or more CD2 antagonists and one or more TNF-α antagonists (*e.g.*, ~~Enbrel™~~ENBREL® (etanercept) and/or ~~REMICADE®~~REMICADE® (infliximab)). In another embodiment, a composition comprises one or more CD2 binding molecules and one or more TNF-α antagonists. In a preferred embodiment, a composition comprises MEDI-507, an analog, derivative or antigen-binding fragment thereof and one or more TNF-α antagonists. In another preferred embodiment, a composition comprises MEDI-507, an analog, derivative or antigen-binding fragment thereof and a soluble TNF-α receptor (*e.g.*, ~~Enbrel™~~ENBREL® (etanercept)) or an

antibody that immunospecifically binds to TNF-α (*e.g.*, ~~REMICADE®~~REMICADE® (infliximab)).

On page 135, please amend the paragraph beginning on line 30 as follows:

In another preferred embodiment of the invention, ~~REMICADE™~~REMICADE® (infliximab) is supplied as a sterile and lyophilized powder for intravenous infusion to be reconstituted with 10 ml sterile water for injection. Each single-use vial of ~~REMICADE™~~REMICADE® (infliximab) contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate and 6.1 mg dibasic sodium phosphate. According to the Physician's Desk Reference (55th ed., 2001), the total dose of the reconstituted product must be further diluted to 250 ml with 0.9% Sodium Chloride Injection, USP, with the infusion concentration ranging between 0.4 mg/ml and 4 mg/ml.

On page 136, please amend the paragraph beginning on line 3 as follows:

In another preferred embodiment of the invention, ~~ENBREL™~~ENBREL® (etanercept) is supplied as a sterile, preservative-free, lyophilized powder for parenteral administration after reconstitution with 1 ml of supplied Sterile Bacteriostatic Water for Injection, USP (containing 0.9% benzyl alcohol). According to The Physician's Desk Reference (55th ed., 2001) ~~Each~~each single-use vial of ~~ENBREL™~~ENBREL® (etanercept) contains 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.

On page 136, please amend the paragraph beginning on line 21 as follows:

The compositions may, if desired, be presented in a pack or dispenser device that may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. In certain preferrred embodiments, the pack or dispenser contains one or more unit dosage forms containing no more than 25 mg ~~ENBREL~~ENBREL® (etanercept), 2.5 mg METHOTREXATE, 100 mg ~~REMICADE™~~REMICADE® (infliximab) and 5 mg/mL VITAXIN™.

On page 140, please amend the paragraph beginning on line 33 as follows:

In one embodiment, the recommended dosage of ~~ENBREL™~~ENBREL® (etanercept) is 0.01 to 10 mg/kg, preferably 0.1 to 10 mg/kg, more preferably 0.1 to 5 mg/kg, and even more preferably 0.5 to 2 mg/kg. In another embodiment of the invention, the recommended

dose of ~~ENBREL™~~ENBREL® (etanercept) is 0.01 to 10 mg/kg/week, more preferably 0.1 to 5 mg/kg/week, even more preferably 0.5 to 2 mg/kg/week. In a most preferred embodiment, the weekly dose is not to exceed 50 mg/week. In preferred embodiments, ~~ENBREL™~~ENBREL® (etanercept) is administered by subcutaneous injection twice a week.

On page 141, please amend the paragraph beginning on line 5 as follows:

In a preferred embodiment of the invention, ~~ENBREL™~~ENBREL® (etanercept) is administered at a dose of about 1 mg to about 50 mg, more preferably about 10 mg to about 40 mg, most preferably about 20 mg to about 30 mg. In certain embodiments, a CD2 antagonist is administered in combination with the administration of 0.1 mg to 1 mg, 1 mg to 5 mg, 5 mg to 10 mg, 10 mg to 15 mg, 15 mg to 20 mg, 20 mg to 25 mg, 25 mg to 30 mg, 30 mg to 35 mg, 35 mg to 40 mg, 40 mg to 45 mg, 45 mg to 50 mg, 50 mg to 60 mg, 60 mg to 65 mg, 65 mg to 70 mg, 70 mg to 75 mg, 75 mg to 80 mg, 80 mg to 85 mg, 85 mg to 90 mg, 90 mg to 95 mg, 95 mg to 100 mg, 100 mg to 105 mg, 105 mg to 110 mg, 110 mg to 115 mg, or 115 mg to 120 mg of ~~ENBREL™~~ENBREL® (etanercept) per week. Preferably, ~~ENBREL™~~ENBREL® (etanercept) is given twice weekly as a subcutaneous injection. Preferably the injections are administered 72 to 96 hours apart. In an embodiment, the injections are administered 36 to 132 hours apart, preferably 48 to 114 hours apart, more preferably 72 to 96 hours apart, even more preferably about 84 hours apart. In a preferred embodiment, the dosage amounts of ~~ENBREL™~~ENBREL® (etanercept) are less than are typical when it is administered alone. See Physicians' Desk Reference (55th ed. 2001). Accordingly, in a preferred embodiment, the administration of a CD2 antagonist is combined with the administration of no more than 25 mg of ~~ENBREL™~~ENBREL® (etanercept). In preferred embodiments, less than 25 mg, less than 20 mg, less than 15 mg, less than 10 mg or less than 5 mg ~~ENBREL™~~ENBREL® (etanercept) is administered per dose. According to the methods of the invention, ~~ENBREL™~~ENBREL® (etanercept) is administered at doses of 1 mg, 1 mg to 5 mg, 5 mg to 10 mg, 10 mg to 15 mg, 15 mg to 20 mg, 20 mg to 25 mg, or 25 mg, twice weekly.

On page 141, please amend the paragraph beginning on line 25 as follows:

In an embodiment of the invention a recommended dose of ~~REMICADE™~~REMICADE® (infliximab) is 0.1 to 10 mg/kg, more preferably 1 to 7 mg/kg, even more preferably 2 to 6 mg/kg, and most preferably 3 to 5 mg/kg. In a most preferred embodiment, the dose does not exceed 3 mg/kg. In certain preferred embodiments,

~~REMICADE™~~REMICADE® (infliximab) is ~~administrated~~administered by intravenous infusion followed with an additional dose at 2 and 6 weeks after the first infusion then every 8 weeks thereafter.

On page 141, please amend the paragraph beginning on line 31 as follows:

In a preferred embodiment of the invention, ~~REMICADE™~~REMICADE® (infliximab) is administered at a dose of about 1 mg to about 600 mg, more preferably about 100 mg to 500 mg, and most preferably about 200 mg to about 400 mg. In certain embodiments of the invention, an integrin $\alpha_v\beta_3$ antagonist is administered in combination with 1 mg to 10 mg, 10 mg to 50 mg, 50 mg to 100 mg, 100 mg to 150 mg, 150 mg to 200 mg, 200 mg to 250 mg, 250 mg to 300 mg, 300 mg to 350 mg, 350 mg to 400 mg, 400 mg to 450 mg, 450 mg to 500 mg, 550 mg to 600 mg, 600 mg to 650 mg, 650 mg to 700 mg, 700 mg to 750 mg, 750 mg to 800 mg, 800 mg to 850 mg, 850 mg to 900 mg, 900 mg to 950 mg, 950 mg to 1000 mg of ~~REMICADE™~~REMICADE® (infliximab), initially and at 2 and 6 weeks after the first dose, and then every 8 weeks after. In preferred embodiments, the dosage amounts for ~~REMICADE™~~REMICADE® (infliximab) are less than are typical when it is administered alone. See Physicians' Desk Reference (55th ed. 2001). Accordingly, in a preferred embodiment, no more than 600 mg of ~~REMICADE™~~REMICADE® (infliximab) is given as an intravenous infusion followed with additional doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. In other embodiments, the additional doses are administered at 1 to 12 weeks, preferably 4 to 12 weeks, more preferably 6 to 12 weeks, and even more preferably 8 to 12 weeks. Preferably, the integrin $\alpha_v\beta_3$ antagonist is VITAXIN™.

On page 149, please amend the paragraph beginning on line 3 as follows:

In a specific embodiment of the invention where the experimental animal model used is adjuvant-induced arthritis rat model, body weight can be measured relative to a control group to determine the anti-inflammatory activity of the combination therapies of invention. Combination therapies tested may include, but are not limited to, combinations comprising any integrin $\alpha_v\beta_3$ antagonist functionally homologous to VITAXIN™, a TNF-α inhibitor, and a chemotherapeutic agent. RENBREL™, the rat homolog of ~~ENBREL™~~ENBREL® (etanercept), which functions as a TNF-α inhibitor, may also be tested in combination therapies in rat models.